I

THE ERADICATION OF REFRACTORY GONOCOCCIC INFECTIONS BY COMBINED ARTIFICIAL FEVER-CHEMOTHERAPY

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"To Keep as Many Men at as Many Guns as Many Days as Possible."
—Mission of the Medical Department of the United States Navy.

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In a communication (1) addressed to the Medical Society for the Study of Venereal Diseases by one of us (Simpson) in 1936, an appraisal was made of the *rôle* of artificial fever therapy ‡ in the management of gonococcic infections. The purpose of the present report is to record the development of new technics for the eradication of gonococcic infections which are refractory to modern chemotherapeutic methods.

The widespread acceptance of sulfonamide compounds as effective agents in the treatment of gonococcic infections has modified the value of all pre-existing types of therapy. The rapidity with which most cases yield to intelligent and controlled administration of these compounds has obviated the necessity for the use of accessory therapeutic agents in such cases. As Harkness (2) has stated so aptly, modern chemotherapy is more of a specific for gonorrhea than are salvarsan and its derivatives for syphilis. The brilliance of such results has been dimmed somewhat by the development of several circumstances which will prevent the ultimate

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‡ The term "artificial fever therapy" denotes the production of fever by physical means.

eradication of the disease: the asymptomatic carrier (3a), the development of chemotherapy-fast strains of the gonococcus (4), and the occurrence of relapse after apparent cure (5). Even in instances in which the individual has received what was thought to be adequate treatment, sulfonamide compounds may fail completely to eradicate the infection. This observation does not imply that sulfanilamide is of limited value in the treatment of gonorrhea; rather, it indicates that even with ideal treatment conditions there will be a considerable proportion of such patients who are not cured by chemicals available at the present time.

The value of artificial fever in the treatment of gonorrhea during the pre-sulfanilamide era has been demonstrated by many investigators (6). Relatively few publications have appeared concerning the effectiveness of artificial fever therapy since the introduction of modern chemotherapy (7). A few recent publications have dealt with the action of artificial fever in cases of gonorrhea refractory to chemotherapy (8).

It is our purpose in this report to point out the value of artificial fever therapy, either alone or combined with chemotherapy, in a series of patients with gonorrhea known to be resistant to sulfanilamide, sulfapyridine or sulfathiazole, or the sequential use of these compounds.

Evolution of Fever Dosage

Treatment of gonococcic infections with artificial fever began in this Institute in 1932 (6a, 9). The first patient so treated was referred for fever therapy because of refractory latent syphilis; he also manifested concurrent clinical and bacteriologic evidence of active gonococcic urethritis and arthritis. During the course of treatment for syphilis, which consisted of five-hour sessions at 105–106 F. (40·6–41·1 C.) given once weekly, the arthritis improved immediately and the signs of urethritis gradually disappeared. Succeeding patients treated primarily for gonococcic arthritis received the same fever dosage (6a).

With the observation of Anderson, Arnold, Trautman and Faget (10), in 1934, that semi-weekly treatments hastened the disappearance of the urethritis, interest shifted from the treatment of gonococcic arthritis *per se* to include the

eradication of the co-existent genital infection. Attention thus became concentrated upon shortening the treatment interval in order to hasten recovery. This plan was quickly adopted by other workers. Desjardins *et al.* (11), in 1935, reported upon the fever treatment of 56 patients with various manifestations of gonococcic infection with semi-weekly five-hour sessions at 105–106 F. (40·6–41·1 C.); after an average of five such sessions, cure was effected. Other workers (6) reported essentially similar results.

It was not until the important researches of Carpenter, Boak, Mucci and Warren (12) upon the thermolability of different strains of gonococci that the foundations were laid for accurate dosage of fever in the treatment of this infection. Unfortunately, the determination of the thermal death time for a given strain of gonococcus and the subsequent regulation of fever dosage according to the thermal death time of each strain had many barriers in the way of its practical application. Such a procedure is not adaptable to routine performance in the average fever therapy clinic. Nevertheless, these researches provided the impetus toward the administration of fever in longer sessions, even if the dosage of fever at one session did not approximate the thermal death time of the organism.

At that time, the inadequate apparatus and the fragmentary knowledge of the physiology of fever did not permit the use of sustained fever at high levels for long periods. Although long sessions of fever at 106–107 F. (41·1–41·7 C.) were given in this earlier period, they were usually regarded as technical feats and were not recommended for the routine treatment of gonorrhea. For this reason, the practice of giving multiple short treatments at 105–106 F. (40·6–41·1 C.) was retained.

With improvements in design of the air-conditioned cabinet (Hypertherm), better insulation, the use of thermostat controls and of electrical indicating or recording rectal thermometers, it was found that longer sessions of fever could be tolerated without difficulty, if administered by skilled workers. These factors, combined with a recognition of the necessity for compensating for sodium chloride and fluid loss, cognizance of the dangers inherent in certain types of sedatives, and the ability to detect warning signals early, have measurably increased

both the safety and comfort requisites for the satisfactory and practicable administration of artificial fever.

Since it has been observed that longer sessions of fever reduced the total number of treatments required, Krusen (13), in 1937, began using ten-hour sessions at 106–107 F. (41·1–41·7 C.) instead of the then standard five-hour to eight-hour treatments at 105–106 F. (40·6–41·1 C.). By this means, he was able to reduce the number of treatments from an average of 5 to 1·1.

In the past, the chief objection raised against the use of artificial fever has been that it is a hazardous undertaking. During recent years, however, the technic of administering artificial fever has progressed to a point at which patients may now receive relatively long sessions at relatively high temperature levels with far more safety and comfort than was possible with shorter sessions at lower temperature levels in former years. In skilled hands, treatments of this type may now be prescribed with a frequency which approaches routine. The great improvements in apparatus and over a decade of constantly broadening experience have contributed to the safety of the undertaking.

Selection of Patients for Fever Treatment

(*a*) *Previous Chemotherapy.*—An earnest attempt has been made to have all of the patients included in this report completely comparable in one respect, namely, resistance or intolerance to chemotherapy. Earlier patients received only sulfanilamide, since sulfapyridine and sulfathiazole were not at that time generally available. Those treated subsequently had received sulfanilamide or sulfapyridine or sulfathiazole, or one of these compounds followed by another. A few individuals had received relatively small amounts of chemotherapy because of the development of one or more of the following untoward reactions: blurred vision, extreme nausea and vomiting, acute hemolytic anemia, granulopenia, fever, hepatitis, jaundice, and dermatitis.

(*b*) *Duration of the Disease.*—Fever therapy has not been limited to any particular manifestation or stage of the disease. Since we dealt with drug-resistant patients, no individual treated had had the disease for less than two weeks. No attempt has been made to classify the

condition as acute, subacute, or chronic on the basis of duration of symptoms. The patients were arbitrarily divided into two groups: those in whom the duration of the disease was more than three months or less than three months. Approximately one-half of the patients fall into each group.

(*c*) *Complications of the Disease.*—No patient was treated for uncomplicated anterior urethritis. All varieties of complications were treated, varying from the relatively minor one of prostatitis to severe pan-pelvic inflammation. Seven patients were completely asymptomatic (so-called "carriers"); each of these individuals had received extensive chemotherapy previously.

(*d*) *Sex.*—Patients of either sex received treatment without selection. There was a sex-distribution ratio of roughly three males to one female.

(*e*) *Age.*—Age alone was no bar to treatment, provided the diagnostic survey revealed no contraindications. The age limits varied from 16 to 56 years, with a mean age of 27 years.

(*f*) *Contacts.* Whenever possible, all suspected "contacts" were examined bacteriologically and clinically. In addition to those found to be obviously infected, seven completely asymptomatic persons yielded positive cultures from secretions of the genital tract.

No patient experienced any ill effects from the combined method of treatment.

Care of the Patient during Hospitalization

The technic by which the earlier treatments were carried out has been described in previous publications (14). The changes which have accrued in our methods within the past two years have been described in detail elsewhere (15).

All patients were hospitalized. Eligibility for fever therapy was determined after a thorough diagnostic survey, which included a careful history, a complete physical examination, and all indicated laboratory procedures. The apparatus employed was the Hypertherm.*

* Manufactured under licence from Dr. Charles F. Kettering and the General Motors Corporation by the Liebel-Flarsheim Company, Cincinnati, Ohio, U.S.A.

Most of the patients received a short preliminary "pilot" treatment, the purposes of which were to test the patient's physiologic responses to fever, and to allay apprehension and to accustom him to lying in a warm, humid environment. The pilot treatment was given at a lower rectal temperature, usually 105 F. (40·6 C.), and was of three hours' duration. The last twenty-two patients included in this report received no preliminary pilot treatment. Their reactions, during and subsequent to the fever treatment, differed in no significant degree from those who also received the pilot treatment. The total period of hospitalization required for the latter group of patients did not exceed forty-eight hours.

Throughout the fever treatment, except for brief rest periods, pure oxygen was supplied by means of the Boothby-Lovelace-Bulbulian (16) nasal mask in quantities sufficient to maintain an alveolar oxygen concentration of 60 per cent. or more. At intervals of three hours, the patient received 50 cubic centimeters of a 50 per cent. solution of dextrose intravenously. No other fluids were given intravenously. He was encouraged to take by mouth 300 to 400 cubic centimeters per hour of iced 0·6 per cent. solution of sodium chloride in tap water. The sedative used was pantopon by hypodermic injection in doses of $\frac{1}{6}$ to $\frac{1}{3}$ grain. Many patients required no sedative and few needed more than one such injection. The cabinet doors were not opened except for intravenous injections, blood pressure recordings, or checking the resistance-wound electrical rectal thermometer with a certified mercury thermometer. The constant inspection of the skin, which in former years was necessary to prevent burns, is unnecessary, since, with the low dry-bulb temperatures now used, burns are unknown and even erythema of a mild degree is not seen.

During each of the succeeding three days, the genital secretions were collected for smears and cultures. Cultures were made on two types of mediums: McLeod's (17) medium and the plasma-agar medium developed by us (18). During the past year only the latter medium was used. Culture mediums were incubated according to Thompson's simplified technic (19) for production of increased carbon-dioxide tension. At the end of twenty-four hours, the cultures were inspected and organisms from oxydase-

positive (20) colonies were stained by Gram's method. If deemed advisable, a pure strain of the organism was isolated and its identity established by fermentation tests.

If the results of the bacteriologic examinations were negative for gonococci, the patient was dismissed and was then followed as an outpatient for at least three months.

Criteria of Cure

The term " cure " is employed in the bacteriologic as well as the clinical sense. The criteria of clinical cure in the male included : complete resolution of the presenting clinical symptoms, absence of pus and shreds of mucus in the urine, restoration of the prostatic fluid toward normal, and failure of the usual " provocative " tests (massage of the peri-urethral glands over a urethral sound, and repeated prostatic massage) to influence the clinical status. It is our observation that little reliance can be placed upon the clinical status alone in determining cure. Seven of the patients treated were asymptomatic from the outset, the diagnosis having been established solely on bacteriologic findings. Since the cultural methods employed have been so dependably accurate, we have relied chiefly on the bacteriologic findings in determining cure. Periodic cultural re-examinations of the genital secretions were carried out for a period of at least three months. In the female, pelvic examinations were done on the first post-menstrual day of each of the three menstrual periods following the treatment.

No patient was included in this series who had not been under observation for at least three months. Some of the patients were followed carefully for from two to to two and one-half years.

Experimental Data

The data accumulated during the course of this experimental study are summarized in the table. For the purposes of this experiment, evaluation of the effectiveness of the method of treatment employed was in terms of cure following a single treatment session.

The series comprises a total of 105 patients who presented complications of gonorrhea and who were either resistant or intolerant to one or more sulfonamide compounds.

The different groups of patients were divided as follows:

1. Those receiving fever alone:
(*a*) Eight-hour session at 106·6 F. (41·4 C.).*
(*b*) Ten-hour session at 106·6 F. (41·4 C.).
2. Those receiving fever in combination with chemotherapy:
(*a*) Ten-hour session at 106·6 F. (41·4 C.) with sulfanilamide administered orally during eighteen hours before fever.
(*b*) Ten-hour session at 106·6 F. (41·4 C.) with sulfanilamide administered intravenously immediately before fever.
(*c*) Ten-hour session at 106·6 F. (41·4 C.) with concomitant Promin administered intramuscularly.
(*d*) Ten-hour session at 106·6 F. (41·4 C.) with Promin administered intramuscularly during eighteen hours before fever.
(*e*) Ten-hour session at 106 F. (41·1 C.) with Promin administered intramuscularly during eighteen hours before fever.
(*f*) Eight-hour session at 106 F. (41·1 C.) with Promin administered orally during eighteen hours before fever.
(*g*) Eight-hour session at 106 F. (41·1 C.) with sulfathiazole administered orally during eighteen hours preceding fever.

1. (*a*) *Those receiving eight-hour session of fever alone.*—Of the nine patients in this group only one (9·9 per cent.) was bacteriologically negative following a single eight-hour session at 106·6 F. (41·4 C.).

(*b*) *Those receiving ten-hour session of fever alone.*—Only seven (63·6 per cent.) of the eleven patients in this group were rid of the infection following a single ten-hour session at 106·6 F. (41.4 C.). Since it may be argued that some or all of these patients were not necessarily resistant to sulfanilamide therapy, either because of insufficient individual doses or because of failure to give the drug during the night, an unselected group of five consecutive patients (not included in the table) were hospitalized for an average period of two weeks. A sufficient quantity of sulfanilamide was given to maintain the blood sulfanilamide level between 10 and 12 mg. per

* All records of temperature refer to rectal temperature levels determined with a constantly indicating electrical thermometer.

100 cubic centimeters for a period of ten days. The dosage employed averaged 120 grains (8 Gm.) daily. At the end of this period all of the five patients still presented active clinical symptoms of gonorrhea, and the genital secretions yielded abundant growths of *Neisseria gonorrhœæ*; all were cured by subsequent fever therapy.

2. (*a*) *Those receiving ten hours of fever at* 106·6 *F.* (41·4 *C.*) *combined with sulfanilamide administered orally during eighteen hours before fever.*—This group consisted of twenty unselected patients of the same type as that comprising the preceding series. All received an average total of 160 grains (10 Gm.) of sulfanilamide in five doses over a period of eighteen hours. Starting at seven o'clock the following morning, eighteen hours after the administration of sulfanilamide was begun, the patients received a ten-hour session of fever at 106·6 F. (41·4 C.). The blood sulfanilamide concentration averaged 12 mg. per 100 cubic centimeters at the time the patient was placed in the cabinet. No sulfanilamide was given during the fever session. No patient demonstrated either clinical or bacteriologic evidence of gonococcic infection after the single combined treatment session.

(*b*) *Those receiving sulfanilamide administered intravenously immediately before ten hours of fever at* 106·6 *F.* (41·4 *C.*)—In an attempt to simplify the administration of sulfanilamide and to avoid awakening the patient at four-hourly intervals during the night before the fever session, sixteen patients were given sulfanilamide intravenously in the form of an 0·8 per cent. solution (in physiologic solution of sodium chloride) the dosage being calculated on the basis of ¾ grain (0·05 Gm.) per pound of body weight. Such dosage was sufficient to produce an average concentration of 15 mg. per 100 cubic centimeters of blood when the treatment was begun. On the basis of prior studies it was thought that the administration of the drug one hour before the fever treatment would allow sufficient time for its complete distribution throughout the fluids of the body.

Of these sixteen patients only thirteen (81·9 per cent.) were cured by the single ten-hour fever session combined with sulfanilamide given intravenously. Hence, we were forced to the conclusion that the mere presence of sulfanilamide in excess of a 1 : 10,000 concentration at the time the fever was given did not wholly explain its

therapeutic action. It appeared to be necessary for the drug to be present in the body fluids for several hours preceding the fever session.

(*c*) *Those receiving Promin administered intramuscularly during ten hours of fever at* 106·6 *F.* (41·4 *C.*).—Promin,* the sodium salt of p,p'-diaminodiphenylsulfone-N,N'-di (dextrose sulfonate), differs from other similar compounds in its high degree of solubility. It is prepared in ampules as a stable 40 per cent. aqueous solution which is suitable for parenteral injection. Because of its extreme solubility it is possible to administer relatively large quantities of the drug in a minimum amount of solvent. For example, 75 grains (5 Gm.) of Promin may be administered in a total solution volume of 12·5 cubic centimeters. Because of such ready solubility in aqueous fluids it was thought that diffusion in the body fluids should be more rapid and complete than is the case with sulfanilamide.

Since the therapeutic efficacy of this compound in the treatment of gonococcic infections was largely undetermined, a series of eleven patients was subjected to the same type of experimental program as that described under 2 (*b*) with the exception that, instead of sulfanilamide being administered immediately prior to the fever treatment, 75 grains (5 Gm.) of Promin were injected intragluteally when the fever treatment was started and every three hours during the treatment. Thus, a total of 300 grains (20 Gm.) of the drug was given during the ten-hour session of fever. Blood Promin concentrations averaged 10 mg. per 100 cubic centimeters for the duration of the treatment. Excretion of the drug following the treatment appeared to be very rapid, since only traces could be found in the blood from twelve to sixteen hours later.

Of the group of eleven patients subjected to this program, only seven (63·6 per cent.) were cured following a single fever session of ten hours at 106·6 F. (41·4 C.). Therefore, it was felt that there were no advantages in the concurrent use of Promin and fever therapy as administered to these patients over a like amount of fever therapy alone.

(*d*) *Those receiving ten hours of fever at* 106·6 *F.* (41·4 C.)

* Promin was supplied by Dr. E. A. Sharp, Director of Clinical Investigation, Parke, Davis and Company, for investigative purposes.

combined with Promin administered intramuscularly during eighteen hours before fever.—Having observed potentiation of the action of sulfanilamide when administered during a period of eighteen hours prior to fever, eleven patients were given Promin during a like interval. A total of 375 grains (25 Gm.) of the compound was given, in divided doses at four-hourly intervals, during the eighteen-hour period prior to the fever session. None was given during the fever treatment. The concentration of Promin in the blood immediately prior to the fever session was 23 mg. per 100 cubic centimeters; at the conclusion of the treatment it averaged 7 mg. per 100 cubic centimeters.

Signs of toxicity were minimal. Headache, nausea, dizziness, confusion and delirium were not encountered. The sense of weakness commonly observed following the long fever session in those patients receiving sulfanilamide was almost completely absent.

All of the eleven patients in this group were cured following the single combined treatment session.

(*e*) *Those receiving Promin administered intramuscularly during eighteen hours before ten-hour fever session at* 106 *F.* (41·1 *C.*).—Having determined an apparently effective time-dosage relationship as regards chemotherapy, it was thought desirable to experiment with a reduction in the height of fever. Consequently, seven successive refractory patients were given Promin intramuscularly in the same manner as in the preceding series [2 (*d*)]. The only change in the program was in the reduction of the maintenance level of fever during the ten-hour period from 106·6 F. (41·4 C.) to 106 F. (41·1 C.).

All of the patients were cured by the single combined treatment session.

(*f*) and (*g*) *Those receiving Promin or sulfathiazole orally during eighteen hours preceding eight hours of fever at* 106 *F.* (41·1 *C.*)—The next step in the experimental program was a reduction in the number of hours of sustained fever at 106 F. (41·1 C.) from ten hours to eight hours. Four patients received Promin orally (a total of 45 grains (3 Gm.), given in capsules in six doses, each of 7·5 grains) during the eighteen hours immediately prior to a single fever session of eight hours at 106 F. (41·1 C.). Eleven patients were given sulfathiazole orally during the eighteen hours immediately preceding the eight-hour

TABLE

		Type of Treatment	Number of Patients	Total Dosage of Chemotherapy (in grains)	Average Blood Concentration in Mg. per 100 cc.		Percentage of Cure
					Before Fever Treatment	End of Fever Treatment	
Fever alone.		8 hours at 106·6 F. (41·4 C.) . . .	9	None			9·9%
		10 hours at 106·6 F. (41·4 C.) . . .	11	None			63·6%
Fever Combined with Chemotherapy.	10 hrs. at 106·6 F. (41·4 C.).	Sulfanilamide orally 18 hrs. preceding fever .	20	160 gr.	12	8	100%
		Sulfanilamide intravenously immediately before fever.	16	¾ gr. per lb. body wt.	15	8	81·9%
		Promin intramuscularly during fever . .	11	300 gr.	10	10	63·6%
		Promin intramuscularly during 18 hrs. preceding fever.	11	375 gr.	23	7	100%
	10 hrs. at 106 F. (41·1 C.).	Promin intramuscularly during 18 hrs. preceding fever.	7	375 gr.	22	8	100%
	8 hrs. at 106 F. (41·1 C.).	Promin orally during 18 hrs. preceding fever.	4	45 gr.	1·6	2·3	100%
		Sulfathiazole orally during 18 hrs. preceding fever.	11	105 gr.	6	3	100%

fever session at 106 F. (41·1 C.). The latter group received an initial dose of 30 grains (2 Gm.) followed by doses of 15 grains (1 Gm.) at intervals of four hours for five doses, making a total of 105 grains (7 Gm.).

It was apparently quite immaterial whether sulfathiazole or Promin was given prior to the fever session, since all of the fifteen patients in the combined group were cured following the single combined treatment session.

Comment

Analysis of the data contained in the table provides several points for discussion. When fever alone was employed, the necessity for prolonged hyperthermia levels was clearly indicated by the disproportionately higher percentage of cures in the ten-hour group as compared with the eight-hour group. The ten-hour period was, therefore, employed at the beginning of these experiments as the basal unit of fever when chemotherapy was combined with fever. Accepting the ten-hour fever as representing a fairly close approximation of the level of treatment efficacy, the addition of chemotherapy produced a higher incidence of cure only when the chemical agent was administered for a period of several hours preceding the institution of fever therapy. Administration of the drug during the fever treatment was apparently of no value. Out of these experiments has developed the principle that the enhancing effect of the chemotherapeutic agent is a latent one, requiring approximately eighteen hours for effective response.

The uniform response of all the refractory patients to eighteen hours of intensive chemotherapy, followed by a ten-hour session at 106·6 F. (41·4 C.) suggested that a unit dosage of fever less than that originally employed might be used with equal therapeutic effectiveness. Accordingly, the ten-hour time interval was retained, but the height of the fever was decreased from 106·6 F. (41·4 C.) to 106 F. (41·1 C.). As shown in the table the therapeutic index remained unaltered. It was quite apparent, however, that the patients tolerated the treatments much more readily when the height of the fever during the ten-hour period was reduced.

Pursuing this clue, the succeeding groups of patients received only eight hours of fever at a level of 106 F.

(41·1 C.), in addition to the administration of the chemotherapeutic compound during eighteen hours prior to the institution of fever therapy. The lessening of the post-treatment sense of weakness in this group was even more striking, even though the therapeutic effectiveness of such a treatment combination remained unaltered. With the reduction of the temperature level to 106 F. (41·1 C.) employment of a preliminary short conditioning or " pilot " treatment was abandoned. The elimination of the trial treatment is economically advantageous since the period of hospitalization is shortened.

In sum, the total period of hospitalization required for the patients in the latter groups did not exceed forty-eight hours. The advantages of effecting a certain cure of gonococcic infection in such a short time are apparent.

The treatment of gonococcic infections by a combination of chemotherapy and artificial fever now assumes a highly practical aspect. The public health implications of such a highly effective method of treatment should not be overlooked. No longer need the soldier or sailor remain on the non-combatant list for weeks or months because of gonorrhea and its complications. The ultimate goal in the control of venereal diseases should be methods which will quickly and surely eliminate the infection. If the undertaking is surrounded with the requisite safeguards as regards trained, skilled and conscientious personnel and efficient apparatus, it now appears to be feasible and practical to recommend the treatment program outlined in this communication as a rapid, safe and effective means of eliminating gonococcic infections which are refractory to sulfonamide chemotherapy.

Summary and Conclusions

1. One hundred and five patients suffering from gonococcic infection resistant or intolerant to chemotherapy, have been treated with artificial fever, either alone or combined with chemotherapy.

2. Of those refractory patients receiving fever therapy alone, only 9·9 per cent. were cured following a single eight-hour treatment at 106·6 F. (41·4 C.); 63·6 per cent. were cured following a single ten-hour treatment at 106·6 F. (41·4 C.).

3. When combined with artificial fever, the effective-

ness of chemotherapy (sulfanilamide, sulfapyradine, sulfathiazole, or Promin) is influenced by the time-dosage relationship with respect to the fever treatment; when administered for eighteen hours preceding the fever treatment, the effectiveness is much greater than when administered immediately prior to or during the treatment.

4. A ten-day period of intensive sulfanilamide therapy prior to fever therapy is without value in sulfanilamide-resistant patients, provided none of the drug is present in the body fluids at the time of the fever treatment.

5. All of thirty-one unselected consecutive patients treated with sulfanilamide or Promin for eighteen hours before a single ten-hour fever session at a rectal temperature of 106·6 F. (41·4 C.) were cured. Equally favourable results were also obtained when the number of hours of fever was reduced to eight and when the rectal temperature level was reduced to 106 F. (41·1 C.) preceded by the administration of Promin or sulfathiazole orally during eighteen hours immediately prior to the single fever session.

6. With the elimination of the preliminary "pilot" fever treatment, and the reduction in the height and duration of fever, the total period of hospitalization did not exceed forty-eight hours.

7. Rigid bacteriologic criteria were employed as the chief basis for the determination of cure.

8. No patient was injured in any way as a result of the combined method of treatment.

9. The combination of a single eight-hour session of artificial fever therapy combined with the administration of adequate sulfathiazole or Promin for eighteen hours prior to the fever treatment appears to be the procedure of choice in the treatment of chemotherapy-resistant gonococcic infection.

10. The implications are apparent in the application of this therapeutic program for the more prompt and certain eradication of gonococcic infection to persons engaged in vital military, naval and industrial pursuits.

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II

INTENSIVE TREATMENT OF GONORRHŒA AND NON-SPECIFIC URETHRITIS WITH SULPHAPYRIDINE * †

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The effectiveness of sulphapyridine in the treatment of gonorrhœa has never been seriously questioned. From the first results were universally good and led naturally to a spirit of extreme optimism which has now given place to the realisation that there are problems still to be solved, not the least of which is the difficult problem of dosage. From the many and varied schemes of treatment which are used it is clear that there is no general agreement as to the routine dosage which will produce the highest proportion of good results while yet avoiding undue toxic effects. Most workers in the subject now stress the importance of a high constant level of blood sulphapyridine maintained by giving larger doses at first followed by smaller doses at short intervals ; and certainly the general experience is that to give small doses at first is to risk disaster in the form of the resistant or " sulphonamide-fast " case. Bowie, Anderson, Dawson and Mackay (1939) were the first to record their experi-

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